LEADING ARTICLE

Is intestinal metaplasia of the stomach reversible?

M M Walker

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Intestinal metaplasia (IM) of the stomach is a risk factor in developing intestinal-type gastric cancer and hence the question of reversibility is vital. There is emerging epidemiological evidence that with long term follow up, IM may be reversible although a combination of antioxidant agents and eradication of *H pylori* may be necessary to achieve this. The pathogenesis of IM is currently being elucidated and it is likely that a combination of bacterial, host, and environmental factors will be shown to lead to IM. In assessing gastric cancer risk, histochemical typing of IM will most probably be replaced by molecular markers.

Correspondence to:
M M Walker, Department of Histopathology, Faculty of Medicine, Imperial College of Science, Technology and Medicine, St Mary's Campus, Norfolk Place, London W2 1PG, UK; mm.walker@ic.ac.uk

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SUMMARY

As intestinal metaplasia (IM) of the stomach is a risk factor in developing intestinal-type gastric cancer, the question of reversibility is vital. The pathogenesis of gastric IM is being investigated and it is likely that a combination of genetic aspects of both *Helicobacter pylori* and the host, and also environmental factors will be shown to cause this precancerous condition. There is emerging epidemiological evidence that with long term follow up (at least five years after *H pylori* eradication) IM may be reversible. Abolition of *H pylori* alone may not be the answer and combination with other chemopreventive agents may be necessary. IM can be elusive and it is necessary to undertake careful endoscopic evaluation and biopsy likely sites (the lesser curve and angulus). In assessing gastric cancer risk, histochemical typing of IM will probably be replaced by molecular markers although neither of these at present provides a better cancer risk index than simple gastritis scores of antral and body mucosa and the mere presence of IM.

IS INTESTINAL METAPLASIA OF THE STOMACH REVERSIBLE?

It is of fundamental importance to answer this question—if IM of the stomach is reversible, therapeutic intervention may be possible but if not, efforts can only be directed at prevention. However, in attempting to solve this issue, two major problems arise. Firstly, is the pathogenesis of IM understood and therefore can intervention halt or reverse progression? Secondly, can we diagnose and monitor the condition with any degree of certainty?

WHAT CAUSES IM AND WHY IS IT IMPORTANT THAT IT IS REVERSIBLE?

Metaplasia is defined as a potentially reversible change from a fully differentiated cell type to another, which implies adaptation to environmental stimuli, and that embryological commitments can be reversed or erased under certain circumstances.[1] Epidemiological studies have shown that IM in the stomach has a high cancer risk and is therefore defined as a precancerous condition—a clinical state associated with a significantly increased risk of cancer. Dysplasia is a precancerous lesion—a histopathological abnormality in which cancer is more likely to occur than in its apparently normal counterpart.[2] For example, a study carried out in two provinces in China with high and low cancer risks showed that the prevalence of IM was much higher in an area with a high risk for gastric cancer.[3]

> "IM in the stomach has a high cancer risk and is therefore defined as a precancerous condition"

Using a gastric cancer risk index, IM was the only criteria associated with the development of intestinal-type gastric cancer in Japan.[4] A long term study concluded that there is an increased risk of gastric cancer in subjects infected with *H pylori*, severe gastric atrophy, body predominant gastritis, or IM.[5] Therefore, if IM is reversible, there are tangible benefits in reduction in gastric cancer risk.

IF IM IS REVERSIBLE WE NEED TO UNDERSTAND THE PATHOGENESIS

Of the different types of metaplasia in the stomach, intestinal-type is the most common and it is associated with *H pylori* infection and bile reflux.[6] Experimentally, irradiation induces IM.[7]

H pylori and IM

H pylori has been implicated as a major cause of IM. Two major studies provide epidemiological evidence for this. In a 10 year follow up of 35 patients with *H pylori*, IM progression was observed in 49% while no IM was seen during this time in non-infected patients.[5] Another study of 2455 individuals showed that IM was present in 43.1% of *H pylori* positive patients compared with 6.2% of uninfected subjects.

> "*H pylori* has been implicated as a major cause of IM"

Atrophic gastritis and IM were strongly associated with *H pylori* and not with aging, leading to the conclusion that with a high prevalence of the

Abbreviations: IM, intestinal metaplasia; COX-2, cyclooxygenase 2; MSI, microsatellite instability.

precursor lesion the risk of development of early gastric cancer will continue to remain high in Japan.[8] However, *H pylori* most likely acts in concert with other factors to promote IM.

Is it all in the genes?

Recently, it has been shown that a variation in host and bacterial genetic background predisposes to the development of IM. There is evidence that IM is associated with cagA, functional oipA in *H pylori*, and IL-1RN 2 allele in patients from Italy,[9] and another study on family risk of gastric cancer showed that first degree relatives of patients with gastric cancer have an increased prevalence of IM, which is strongly confined to those with *H pylori* infection.[10]

Other promoters of IM

These include lack of vitamin C and cigarette smoking.[11] The concept of atrophy, subsequent hypochlorhydria with bacterial overgrowth, and nitrate generation that damage DNA must also be considered. A European study showed that patients with IM had a significantly higher proportion of gastric juice samples containing bacteria and nitrite and had a gastric pH >6.[12] The role of hypochlorhydria is interesting; studies in rats with IM induced by irradiation showed reversal following lowering of gastric pH.[13] Bile is also a major factor in promotion of IM. An early study from Leeds showed that after stratification for previous surgery, age, and *H pylori* status, the histological feature most strongly associated with bile reflux was IM, including all subtypes.[6] Bile in combination with *H pylori* in rats promotes cyclooxygenase 2 (COX-2) expression in body mucosa and when bile was added, COX-2 expression in histologically normal appearing body mucosa was associated with cell proliferation, atrophy, and IM in the antrum.[14] Sung *et al* also showed that both premalignant and malignant gastric lesions in human subjects demonstrate high COX-2 expression. Successful eradication of *H pylori* caused downregulation of COX-2 expression but failed to reverse IM at one year.[15]

EPIDEMIOLOGICAL EVIDENCE OF REVERSAL OF IM

Does *H pylori* eradication reverse IM?

While this issue has been addressed extensively, there is no concerted view on regression following eradication of *H pylori*.[16] A randomised one year follow up study reported that *H pylori* eradication was beneficial in preventing progression of atrophy and IM of the gastric mucosa[17] and recent presentation of the results of this study at five years has reinforced these findings,[18] although other studies are less conclusive. In a 2–4 year prospective study there was no significant change in antral IM during four years of follow up although antral atrophy declined significantly in the period from 1 to 3 years of follow up [19]. However, a recent report from Japan demonstrated that there are more studies showing regression following eradication therapy than progression.[20] Long term studies are necessary to answer this question and a recent review of the literature shows these are lacking.[18]

Additional intervention strategies to reverse IM

As it is unlikely that *H pylori* is solely responsible for induction and progression of IM, other interventions may be necessary to reverse this condition. In an Italian study, co-administration of ascorbic acid with *H pylori* eradication significantly resolved IM of the gastric mucosa, and the authors concluded that chemoprevention treatment should be considered.[21]

> "Co-administration of ascorbic acid with *H pylori* eradication significantly resolved IM of the gastric mucosa"

Similarly, Correa *et al*'s study in Colombia has shown that effective anti-*H pylori* treatment and dietary supplementation with antioxidant micronutrients may interfere with the precancerous process, mostly by increasing the rate of regression of cancer precursor lesions.[22]

Molecular events

At the molecular level, the sequence of events is under investigation. Microsatellite instability (MSI) is a genetic anomaly in tumours and identified when alleles of novel sizes are detected in microsatellite sequences derived from cancer DNA that are not present in normal tissues of the same individual. These can be detected in IM and the progressive accumulation of MSI in areas of IM may contribute to gastric cancer development.[23] MSI can be shown to be due to epigenetic silencing of the *hMLH1* gene caused by hypermethylation of a CpG island in the promoter region and was found recently to be an important cause of mismatch repair deficiency in sporadic gastric cancer.[24] Cyclins and cyclin dependent kinase inhibitors play a crucial role in the control of cell cycle transitions. Enhanced expression of cyclin D2 and reduced expression of p27 have been implicated in the pathogenesis of cancer, and over expression of cyclin D2 and reduced expression of p27 are closely linked to *H pylori* associated IM. Eradication of *H pylori* infection reverses the aberrant expression of cyclin D2 and p27 in IM.[25] These are potential areas for interventional strategies.

> "Expression of *CDX2* may trigger the initiation and development of IM in the stomach"

In the gastrointestinal tract, homeobox genes regulate the renewal of epithelium at given locations. *CDX1* and *CDX2* genes are intestinal transcription factors that regulate proliferation and differentiation of intestinal epithelial cells and the *CDX1*/2 protein is predominantly expressed in the small intestine and colon but not in the normal adult stomach. These genes also have an important role in tumorigenesis.[26] In IM, expression of *CDX2* precedes those of *CDX1*, sucrase-isomaltase, other intestine specific genes (human defensin 5, alkaline phosphatase), and MUC2 during progression of IM. These findings imply that expression of *CDX2* may trigger the initiation and development of IM in the stomach.[27]

What switches on *CDX1/2* genes in the stomach? The key here is possibly mesenchymal alteration.[28] The inflammatory response to *H pylori* is also sited in mesenchyme and therefore if this stimulus is removed do these genes switch off? In a recent study from Japan, CDX2 expression in the gastric mucosa was found in patients with chronic gastritis and closely associated with IM.[29] However, *CDX2* expression in IM or gastric epithelial cells did not disappear after eradication of *H pylori*. However, this study examined expression of *CDX2* only one year after eradication and may be too short a time course to assess regression of IM, emphasising that this is a slow process. Although neutrophils clear soon after eradication therapy, chronic gastritis and lymphoid aggregates persist at least up to one year[30] and long term studies are needed to evaluate regression of IM in relation to the chronic inflammatory response.

HOWEVER, A MAJOR PROBLEM IN DETERMINING IF IM IS REVERSIBLE IS SAMPLING

Diagnosis: is IM identifiable at endoscopy?

IM is recognisable if it is extensive and the endoscopist is experienced. Biopsy should therefore be from sites that show the typical appearance of whitish plaques, patches, or homogeneous discolouration. The accuracy of endoscopic diagnosis in IM was shown to be 71.3% in a study from Taipei.[31] Another endoscopic method of evaluation is dye endoscopy using methylene blue (methylthioninium chloride). This technique, although described, is not in widespread use. A Japanese study showed it was valuable in assessing regression of IM[32] but it is doubtful that time constraints of endoscopists allow this detailed type of examination.

Diagnosis: where to biopsy?

Sampling errors also beleaguer the histological diagnosis of IM but with the advent of more powerful endoscopes, this problem may resolve. In routine practice, where should biopsies be taken? The Sydney system for grading gastritis provides practical guidelines for optimal biopsy sampling of the stomach, visual analogue scales for grading histopathological features, and formulation of a comprehensive standardised diagnosis.[33] A large study from Houston showed that IM was missed in more than 50% of biopsies from "Sydney sites" in patients with confirmed IM on multiple site sampling and concluded that current and future studies that use the Sydney system as a basis for detecting IM are not likely to be reliable.[34] However, the extent and location of IM—along the lesser curvature (from the cardia to the pre-pyloric zone)—may identify patients with the highest cancer risk.[35] The angulus is an interesting transformation zone and "antralisation" of the gastric incisura is a common event in *H pylor*i infected patients and appears to be associated with an increased risk of atrophic gastritis and IM.[36]

> "It is likely that molecular markers will overtake histochemical evaluation of IM"

Is typing of IM important? A recent study has shown a high prevalence of type III IM in the general population (4%) and indicates that its role as a precursor of gastric carcinoma may have been overemphasised.[37] Critical reviews have found many exceptions to given types of IM as precursor lesions of cancer.[38] It is likely that molecular markers will overtake histochemical evaluation of IM.

To identify IM requires careful endoscopic evaluation of "risk" areas (that is, the lesser curve) and assessment of extent. Substitute measures of gastric cancer risk include simple histological features such as grade of body gastritis. In 50 *H pylori* infected gastric carcinoma patients, the grade of body gastritis was significantly higher than in matched *H pylori* positive control subjects and IM occurred significantly more often in the antrum of carcinoma patients.[39]

CONCLUSIONS

In the long term, with follow up of at least five years, there is epidemiological evidence that IM may be reversible although a combination of antioxidant agents and eradication of *H pylori* may be necessary to achieve this. The pathogenesis of IM is currently being elucidated and it is likely that a combination of bacterial, host, and environmental factors will be shown to lead to IM. There are few studies on the role of acid and/or bile and the pathogenesis of IM—this may be a productive area for future research. IM has widespread implications as metaplasia precedes dysplasia and cancer in many tumours. IM can be elusive to sample unless careful endoscopic evaluation is carried out. In assessing gastric cancer risk, histochemical typing of IM will most probably be replaced by molecular markers although neither of these at present provides a better index than histological scores of gastric antral and body mucosa and the presence of IM.

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